Deciphering Antitumour Response and Resistance With INtratumour Heterogeneity

Darwin II

STUDY DESIGN & AIM

DARWIN2 is a phase II, multi-centre, non-randomised, molecularly stratified trial for NSCLC patients to study tumour heterogeneity using genomic analysis.

This trial aims to explore whether mutational burden and neo-antigen repertoire predict for improved progression free survival with anti-PDL1 mAb immunotherapy for those patients with stage IIIB/IV NSCLC (in patients whose tumour lacks an actionable mutation).

For those patients with actionable BRAFV600 mutations, HER2 amplification and HER2 IHC 3+ or ALK/RET gene fusions this trial aims to assess the role of clonal dominance on the mechanism of action and response to vemurafenib, trastuzumab emtansine and alectinib respectively.

ENDPOINTS

Primary Endpoint:

- To compare the efficacy of MPDL3280A (Atezolizumab), as measured by investigator-assessed progression free survival according to:
  - I. Intra-tumour heterogeneity as assessed using an intratumour heterogeneity score
  - II. Genomic instability as assessed using a weighted genome instability index (wGII)
  - III. Neo-antigen burden
  - IV. Mutational burden
- PFS is defined as the period between the date of registration to the date of progression or death (whichever occurs first)
- Overall Survival (OS is defined as the time between the date of enrolment and the date of death due to any cause)

Secondary Endpoints:

- ORR – Investigator assessed according to RECISTv1.1
- Other time to event outcomes, including time to progression, disease free survival and duration of response, disease control benefit (>6 months)
- Toxicity, including dose reductions, interruptions modifications and exposure

TISSUE AND BLOOD SAMPLES

- Biopsy of site of recurrence (consented as part of TRACERx for applicable patients; for non-TRACERx consent must first be obtained) prior to starting any treatment. Non-TRACERx patients must have two tissue/DNA samples of their disease available.
- Biopsy at progression (if patient consents)
- cfDNA plasma samples at pre-cycle 1 (baseline), post-cycles 2, 4, 6, 8, 12, 16, 20, at end of treatment, and on progression for patients on Arm 1
- cfDNA plasma samples at pre-cycle 1 (baseline), post-cycles 1, 2, 4, 6, and every 3 cycles thereafter, and on progression for patients on Arms 2, 3 or 4
- CTC blood samples at pre-cycle 1 (baseline), post-cycle 2 and progression for all patients

Please refer to the DARWIN2 protocol and laboratory manual and for details.
Please note: additional samples are also required as part of the TRACERx study. Please refer to the TRACERx protocol, trial specific procedures and samples summary for details.

SUMMARY OF ELIGIBILITY CRITERIA

- Multi region sequencing data of the primary tumour available. Non-TRACERx patients must have two tissue/DNA samples of their disease available
- Must be willing to have biopsy of relapsed disease prior to starting any treatment
- Arm 1: Absence of any actionable mutation
- Arm 2: Presence of BRAFV600 mutation
- Arm 3: Presence of ALK/RET gene fusion and ALK IHC+
- Arm 4: Presence of HER2 amplification and HER2 IHC 3+ only
- Absence of sensitizing EGFR mutation (see protocol for exceptions)
- ECOG performance status 0-2 for Arms 1-3, or 0-1 for Arm 4
- Measurable disease by RECIST v1.1. Patients without measurable disease may be eligible following discussion with the CI and UCL CTC
- Anticipated life expectancy of at least three months
- Able to swallow and retain oral medication (Arms 2&3)
- Adequate organ function
- Unsuitable for radical radiotherapy
- No anti cancer therapy within 14 days prior to registration (other than MPDL3280A (Atezolizumab))
- No palliative radiotherapy within 1 week prior to registration
- No pre-existing auto immune disease (some exceptions allowed)
- No current or pre-existing interstitial lung disease
- No known hypersensitivity to any study IMP or to any of the excipients
- No known HIV, HBV, HCV or syphilis infection
- No history of other malignancy (see protocol for exceptions)
- No symptomatic brain metastases
- No severe symptomatic arrhythmias (excluding atrial fibrillation)
- No cardiac abnormalities
- No conditions that may preclude informed consent or protocol compliance
- No pregnant, lactating or actively breastfeeding females
- Patients of childbearing potential/able to father a child must be willing to use highly effective contraceptives during the trial and for one month after end of treatment
- Arm 1: No treatment with corticosteroids or other systemic immunosupressive medications 2 weeks prior to registration, or anticipated requirement for such medications during the trial (see protocol)
- Arm 2, 3 and 4: No patients taking medication known to prolong QT interval 2 weeks prior to registration
- Arm 2: Previous BRAF inhibitor therapy

Please refer to the DARWIN2 protocol for full list of inclusion/exclusion criteria

CONTACT DETAILS

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Sponsor: University College London
Funder: F. Hoffmann-La Roche Ltd

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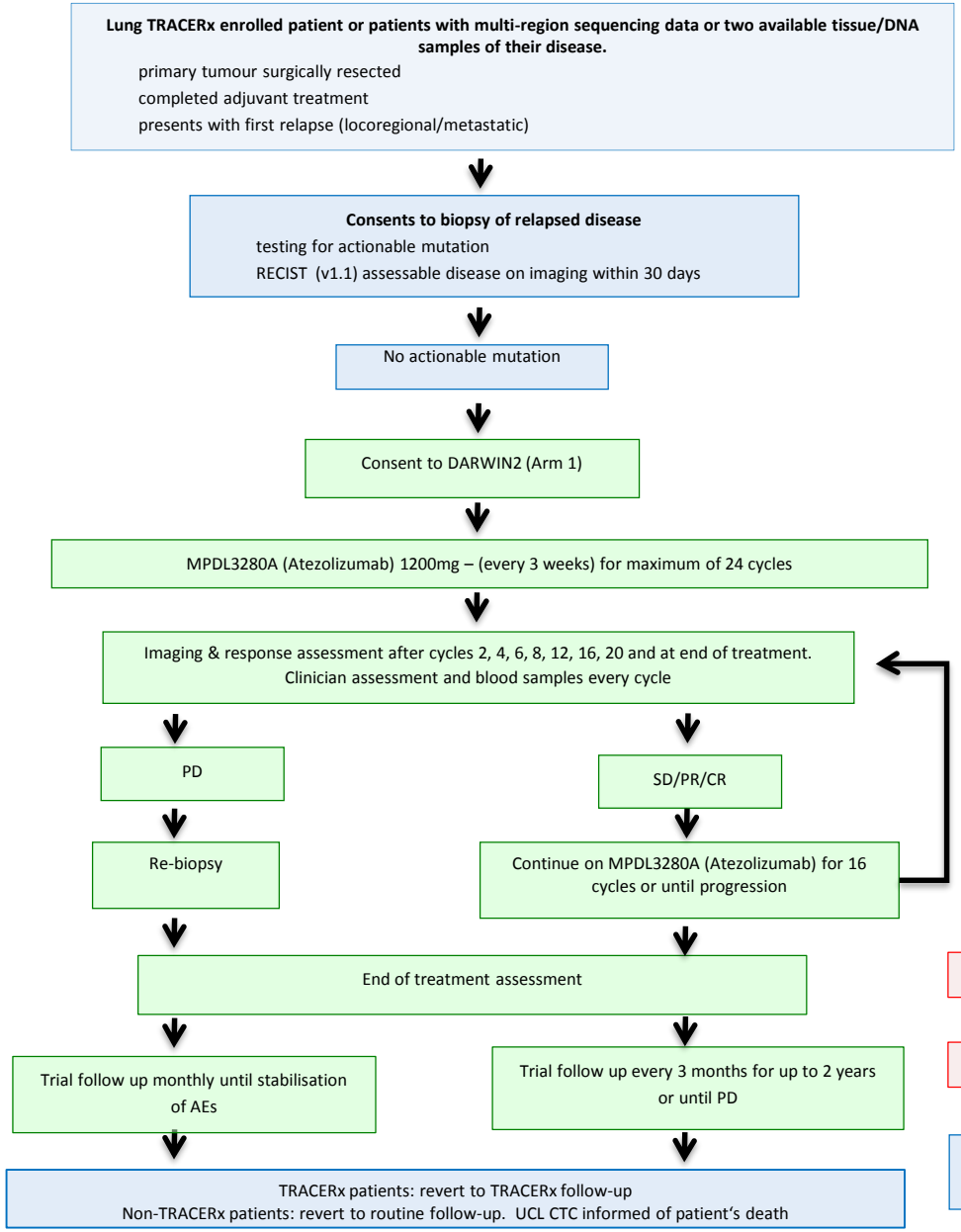
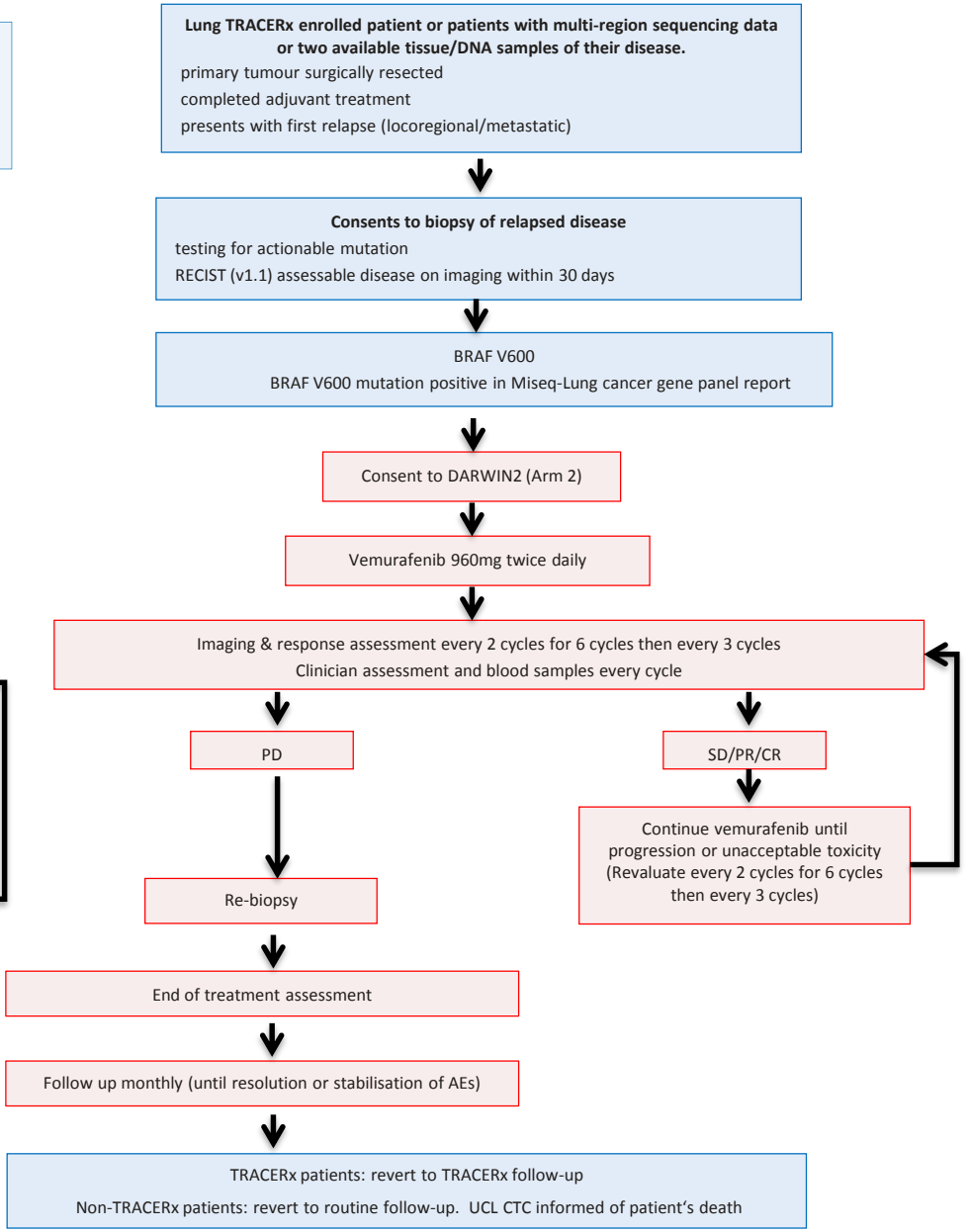
NCRI National Cancer Research Institute

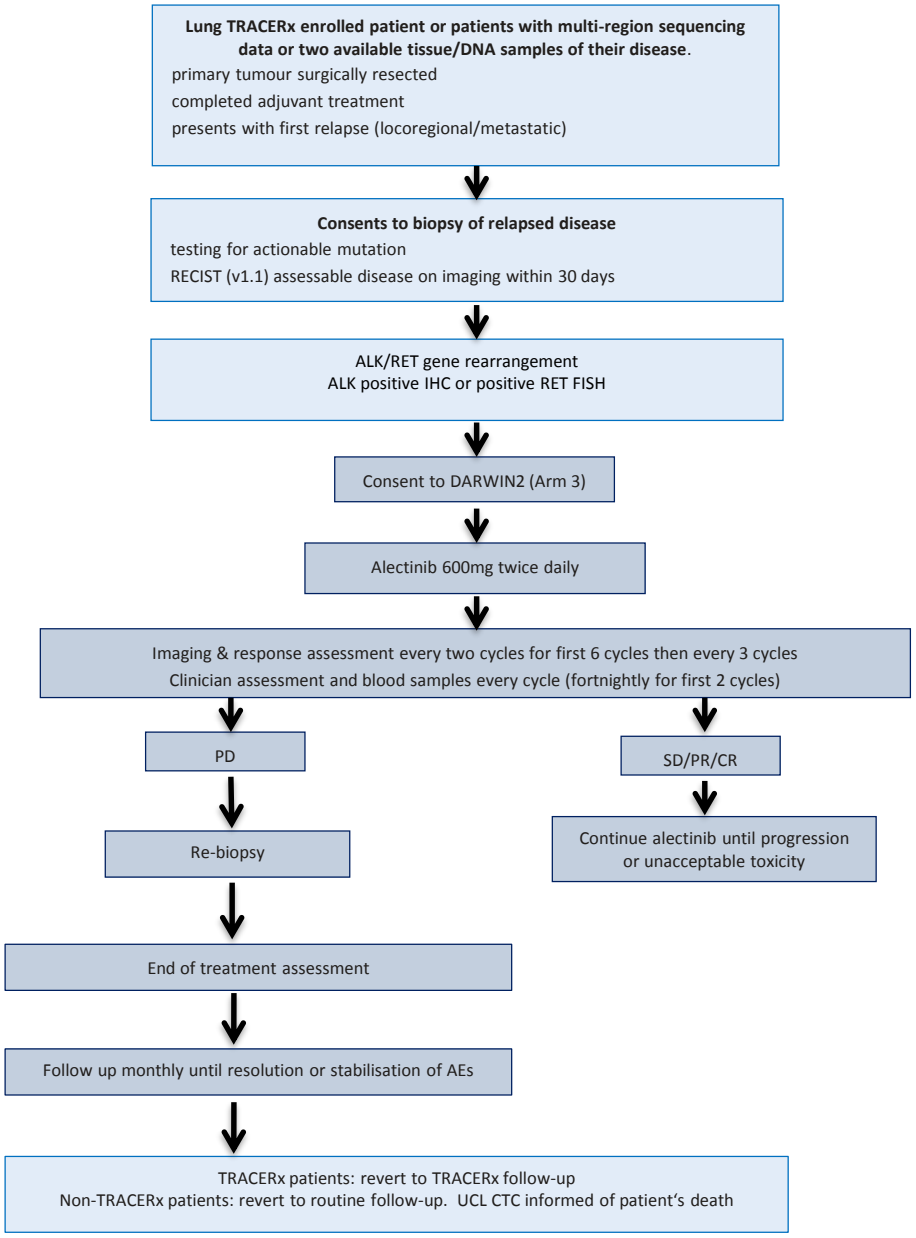
Arm 1:
No actionable mutation



Actionable mutation: Arm 2 – BRAFV600:



Actionable mutation: Arm 3 – ALK/RET gene rearrangement:



Actionable mutation: Arm 4 – HER2 amplification and HER2 IHC 3+: